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Research article

Correlations between growth differentiation factor 15 (GDF-15) serum levels and gene polymorphism with type 2 diabetes mellitus

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ABSTRACT

Purpose: To date, the relationship between Growth Differentiation Factor 15 (GDF-15) gene polymorphism and the risk of type 2 diabetes mellitus (T2DM) has not been clarified. Our study aims to explore the association between serum GDF-15 levels and related gene polymorphism with the risk of T2DM in a Chinese rural Yao population.

Methods: This was a 1:1 case-control study with 179 T2DM patients and 179 age- and sex-matched control participants. Serum GDF-15 levels were measured by enzyme-linked immunosorbent assay, and polymorphisms (rs1059519, rs1059369, rs1804826 and rs1054564) were genotyped by MassArray mass spectrometry.

Results: Serum GDF-15 (sGDF-15) levels were higher in patients with T2DM and glycosylated hemoglobin (HbA1c) $\geq$ 6.5 % compared to that in controls ($p < 0.001$). The area under the curve (AUC) corresponding to sGDF-15 levels was 0.626. Serum GDF-15 was positively correlated with fasting plasma glucose (FPG) ($r_s = 0.150$, $p < 0.001$) and HbA1c ($r_s = 0.160$, $p < 0.001$). The frequency of GDF-15 gene rs1054564 GC + CC genotype was significantly associated with increased risk of T2DM compared to GG genotype (OR = 1.724, 95CI: 1.046–2.841, $p = 0.033$). Frequencies of rs1804826 T allele (β additive = 113.318, $p = 0.026$) and rs1054564 C allele (β additive = 247.282, $p = 0.001$, β dominant = 286.109, $p = 0.001$) was significantly correlated

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with higher sGDF-15. The rs1059519 C allele was negatively correlated with FPG (β recessive = −0.607, $p = 0.047$) and HbA1c (β recessive = −0.456, $p = 0.020$).
Conclusion: Serum GDF-15 levels were positively correlated with FPG and HbA1c. The GDF-15 rs1054564 GC + CC genotype was associated with a significantly higher T2DM risk. The rs1059519 C allele was negatively correlated with FPG and HbA1c.

1. Introduction

Type 2 diabetes mellitus (T2DM) accounts for 90 % of diabetes cases [1]. T2DM can cause a series of complications, such as retinopathy, nephropathy, and neuropathy, as well as ischemic heart disease, stroke, and even lead to disability and death. Fasting plasma glucose (FPG) has been the gold standard for the diagnosis of T2DM [2], and HbA1c detection is another important component of the T2DM diagnosis [3]. Diabetes affects 537 million people globally, with this number projected to rise to 783 million by 2045 [4]. In China, there are approximately 111.4 million diabetic aptients and 48.6 million predabetic patients [5].

Growth differentiation factor-15 (GDF-15), also known as macrophage inhibitory factor-1 (MIC1) and non-steroidal anti-inflammatory drug-activated gene-1 (NAG1) [6], was first identified in 1997, is a member of transforming growth factor-beta (TGF-β) superfamily, which plays multiple roles in a variety of cellular processes [7]. The human GDF-15 gene is located on chromosome 19p12–13.1 and consists of two exons and one intron. GDF-15 is considered a marker of inflammation and oxidative stress, which is widely expressed in liver, skeletal muscle, kidney, heart or macrophage, is a direct molecular target of p53 protein and induced by tissue injury, hypoxia and pro-inflammatory cytokine response [8]. Frimodt-Møller M et al. [9] found that higher GDF-15 levels could be used to independently predict all-cause mortality in T2DM patients. Compared with the normal group, mice injected with GDF-15 showed increased body weight and decreased blood sugar, while GDF-15 significantly improved T2DM mice polydipsia, polyphagia, polyuria and listlessness. Cross-sectional studies have shown that circulating GDF-15 levels are positively correlated with insulin resistance (IR) [10]. However, in prospective studies of obese/T2DM patients after bariatric surgery, circulating GDF-15 levels were further increased when IR was significantly improved [11,12]. Although several studies have confirmed that serum GDF-15 levels are associated with the risk of T2DM, there are few studies on the relationship between GDF-15 related single nucleotide polymorphisms (SNPs) and the risk of T2DM.

This study aims to evaluate the association of serum GDF-15 levels with T2DM and blood glucose metabolic indexes, and further explore the association of GDF-15 gene polymorphism (rs1059519, rs1059369, rs1804826, rs1054564) with T2DM risk and blood glucose metabolic indexes in a Chinese rural Yao population from Gongcheng Yao Autonomous County in northeast of Guangxi, China.

2. Methods

2.1. Study population

In this case-control study, participants were from residents of the Guangxi Eco-Environmental Health and Aging Study (GEHAS) who participated in the study baseline from December 2018 to December 2019. The following criteria were followed:a) residents of the study area aged 30 years or older; b) years of local residence ≥ 5. We also excluded individuals who met the following criteria: a) incomplete questionnaires; b) lack of FPG, HbA1c, or other clinical data; c) those with severe combined cardiac, hepatic, renal, and other vital organ insufficiencies; d) individuals with cancer or were undergoing anticancer treatment; e) diagnosed with type 1 diabetes. Following these exclusions, we included 3194 individuals in the population baseline dataset. A total of 179 cases of T2DM were identified in the baseline dataset (179/3194, with prevalence of T2DM is 5.50 %), according to diagnostic criteria of T2DM [FPG $\geq$ 126 mg/dl (7.0 mmol/l) or HbA1c $\geq$ 6.5 % (48 mmol/mol) or a history of diabetes or taking antidiabetic medications]. Subsequently, control individuals were randomly matched by sex and age (±5 years) in a 1:1 ratio from the remaining population using "matching function" in SPSS software. A total of 358 individuals aged 30–91 years were enrolled to the final case-control study.

This study was approved by the Medical Ethics Committee of Guilin Medical University (No: 20180702-3). Written informed consent was obtained from all participants prior to the study.

2.2. Data collection

In this study, we conducted face-to-face interviews using a baseline questionnaire that was both standardized and crafted by experts on our research team. Investigators who had undergone uniform training administered the interviews, thereby ensuring the collection of data that was both consistent and reliable. A comprehensive set of demographic data was collected, including gender, age, education, marital status, occupation, smoking status, drinking status, disease history, and physical activity etc. Physical examinations were conducted to accurately measure height, weight, waist circumference, blood pressure, and other relevant data. Body mass index (BMI) was calculated from height and weight (kg/m^2). The automatic clinical chemistry analyzer (Hitachi 7600-020, Kyoto, Japan) was used to detect Fasting venous blood of the subjects to obtain Fasting plasma glucose and blood biochemical indicators. FPG), glycosylated hemoglobin (HbA1c), serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), as well as subsequent DNA sample extraction.

2.3. Measurement of serum GDF-15 levels

The quantitative determination of GDF-15 levels in human serum was performed using an enzyme-related immunosorbent assay kit (DGD150, R&D System, USA) in strict accordance with the kit instructions. All reagents were brought to room temperature before use. The 50 μL tested serum sample was diluted 4-fold with 150 μL RD5-20 calibrator diluent for subsequent detection. The standard curve was created using the four-parameter logic (4-PL) curve fitting, and the corresponding concentration of each sample was calculated by the best fitting curve. The minimum detectable dose of the R&D assay kit used in this experiment was 2.0 pg/mL, with coefficient of variation (CV) ranges of 10.9–1.1 % and 4.1–3.0 % within and between groups, respectively.

2.4. DNA extraction

DNA was extracted by adsorption column method from peripheral blood samples obtained from each participant according to manufacturer's instruction (Ailai Biotechnology Co., Ltd, Beijing, China). In order to ensure the accuracy of SNP typing, the concentration of extracted DNA should be greater than 50 ng/μL, with a total amount exceeding 1 μg. Furthermore, the absorbance ratio met the condition that of 206/230 $>$ 1.4, and 260/280 within the range of 1.7–2.0.

2.5. Determination of the GDF-15 genotype and related SNPs

First, bioinformatic resources (HapMap, ENCODE, 1000 Genomes, etc.) were employed to identify functional SNPs, which are located in gene regulatory regions, coding regions, or regions known to be associated with disease. Second, the aim was to identify SNPs that may affect gene expression. Furthermore, the objective was to combine SNPs that have been reported to be significantly associated with a disease or trait in previous studies. Finally, disease databases and genetic variation databases (e.g., SNPinfo, Ensembl, GWAS Catalog) were utilized for comparisons. Consequently, four SNPs including rs1059519, rs1059369, rs1804826, and rs1054564 were selected. Primers design and SNP typing experiments were conducted by Beijing Bomiao Biotechnology Co., LTD. MassArray flight mass spectrometry system was used to detect SNPs typing. The minimum allele frequency (MAF) of each point was greater than 0.05, which indicated non-low frequency variation. The sequence information is shown in Table S1.

2.6. Definition

Base on the World Health Organization diagnostic criteria [13], T2DM was defined as:FPG $\geq$ 126mg/dl (7.0 mmol/l) or oral glucose tolerance test (OGTT) 2-h blood glucose value $\geq$ 200 mg/dl or HbA1c $\geq$ 6.5 % (48 mmol/mol) or a history of diabetes or taking antidiabetic medications. Marital status was divided into two categories: married (married or cohabiting), non-married (widowed, divorced, separated). According to the years of education, the educational level was divided into three categories: primary school and below, junior high school, high school and above. Physical activity was measured according to labor status in the previous year: light (mainly sitting, standing, or not working normally), moderate (mainly general physical activity), vigorous (mainly manual labor). Hypertension was defined as systolic blood pressure (SBP) $\geq$ 140 mmHg and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg. Body mass index (BMI) was calculated as weight (Kg)/height (M^2), and a continuous variables were included in the analysis.

2.7. Statistical analysis

Categorical data were presented as n (%), with group comparisons conducted using the Chi-square test or Fisher's exact test. Continuous variables adhering to a normal distribution were expressed as mean $\pm$ SD, and comparisons between groups were made using the T-test. Data that did not follow normal distribution were presented as the median M (P25, P75) and analyzed using the Mann-Whitney *U* test; the Wilcoxon rank-sum test was employed for comparing serum GDF-15 levels between groups. The receiver operating characteristic (ROC) curve was generated to evaluate the potential of serum GDF-15 levels as a diagnostic marker for T2DM. Correlations among GDF-15, FPG, HbA1c, BMI, TG, TC, LDL-C, HDL-C were conducted by Spearman correlation test. MAF statistics and Hardy-Weinberg Equilibrium (HWE) test were performed on the SNP sequencing population. When MAF$>$0.05, the mutation type of the SNP site alleles belongs to common variation, and the Harwin equilibrium PHWE$>$0.05 was consider to indicate confirmation to genetic balance. Logistic regression was used to explore the relationship between serum GDF-15 levels, GDF-15 genotypes, and T2DM risk among dominant, recessive, and co-dominant models. Furthermore, linear regression model was performed to assess the correlation between serum GDF-15 levels, FPG, HbA1c and the SNPs. We exclude participants aged 50 years for sensitivity analysis.

All statistical analyses were implemented based on SPSS software (version 25.0) and PLINK software (version 1.90). A *p*-value$<$0.05 (two-tailed) was considered statistically significant.

3. Result

3.1. Population characteristics

A total of 358 subjects were include in the case-control study, with an average age of 64.97 $\pm$ 8.99 years, among Whom individuals aged 50–69 years accounted for the highest proportion of participants (63.41 %). Baseline data demonstrated that FPG and HbA1c in the T2DM group were significantly higher than those in controls ($p < 0.001$), and the proportion of hypertension in case group (88.27

%) was higher than that in control group ($\chi^2 = 14.775, p < 0.001$). The distributions of age, gender, Ethnicity, marital status, education level, smoking, drinking, physical activity and BMI were found to be balanced and comparable between case and control group ($p > 0.05$), as shown in Table 1.

3.2. Increased serum GDF-15 levels in T2DM patients

The mean serum levels of GDF-15 (sGDF-15) in cases and controls were 1074.15 (812.64,1517.43) pg/mL and 878.99 (623.53,1238.61) pg/mL, respectively. There was a statistically significant increase in sGDF-15 levels in cases compared to controls ($p < 0.001$), as illustrated in Fig. 1 (A). We further divided the subjects into two groups by HbA1c equals 6.5 %, and the sGDF-15 levels that in ≥6.5 % of HbA1c group had higher sGDF-15 levels than those with HbA1c <6.5 % ($p < 0.001$), shown in Fig. 1 (B). ROC analysis indicated that the AUC was 0.626 (95 % CI: 0.569–0.684, $p < 0.001$) when serum levels of GDF-15 in T2DM patients were compared to that in controls (Fig. 2A). Spearman correlation analysis revealed that sGDF-15 levels were significantly positively related to FPG ($r_s = 0.150, p < 0.01$) and HbA1c ($r_s = 0.160, p < 0.01$), and negatively correlated with TC ($r_s = -0.111, p < 0.05$) and LDL-C ($r_s = -0.150, p < 0.01$). There was no significant correlation between the selected SNPs and BMI, TG and HDL-C levels ($p > 0.05$) (Fig. 2B).

We further divided participants into four quartile groups (Q1 to Q4) based on sGDF-15 levels for logistic regression analysis. After adjusting for age, gender, smoking, drinking and hypertension, we found that compared with Q1, Q2-Q4 groups all exhibited an increased risk of T2DM, and the ORs (95%CI) were 3.183(1.665–6.085), 4.067(2.078–7.962) and 6.246 (3.033–12.862), respectively, with all $p < 0.001$ (Table 2).

3.3. Relationship between GDF-15 gene polymorphisms and T2DM risk

The GDF-15 gene is located on chromosome 19, and the SNP loci that were successfully classified in this study were rs1059519, rs1059369, rs1804826 and rs1054564. The MAF of each point was greater than 0.05, which belonged to non-low frequency variation. The mutant alleles above were C, A, T, and C. Both the T2DM case group and control group demonstrated compliance with the HWE

Table 1
Demographic characteristics of case-control population.

Variables	Overall (n = 358)	T2DM n (%)		χ^2/t	p
		control (n = 179)	cases (n = 179)		
Gender				0.000	1.000
Male	154 (43.02)	77 (43.02)	77 (43.02)		
Female	204 (56.98)	102 (56.98)	102 (56.98)		
Age, years	64.97 ± 8.99	65.59 ± 9.07	64.36 ± 8.89	1.295	0.196
Age groups				0.120	0.942
<50	23 (6.42)	12 (6.70)	11 (6.14)		
50~69	227 (63.41)	112 (62.57)	115 (64.25)		
≥70	108 (30.17)	55 (30.73)	53 (29.61)		
Ethnicity				4.144	0.126
Han	107 (29.89)	62 (34.63)	45 (25.14)		
Yao	234 (65.36)	108 (60.34)	126 (70.39)		
Else	17 (4.75)	9 (5.03)	8 (4.47)		
Marital status				0.782	0.377
Married	81 (22.63)	44 (24.58)	37 (20.67)		
Non-married	277 (77.37)	135 (75.42)	142 (79.33)		
Education level				2.847	0.241
Primary or less	269 (75.14)	139 (77.65)	130 (72.63)		
Junior school	68 (18.99)	28 (15.64)	40 (22.34)		
High school	21 (5.87)	12 (6.71)	9 (5.03)		
Smoking				1.903	0.168
No	294 (82.12)	142 (79.33)	152 (84.92)		
Yes	64 (17.88)	37 (20.67)	27 (15.08)		
Drinking				1.028	0.311
No	241 (67.32)	116 (64.80)	125 (69.83)		
Yes	117 (32.68)	63 (35.20)	54 (30.17)		
Physical activity				0.563	0.755
Light	195 (54.47)	98 (54.75)	97 (54.19)		
Medium	155 (43.30)	76 (42.46)	79 (44.13)		
Vigorous	8 (2.23)	5 (2.79)	3 (1.68)		
Hypertension				14.775	**<0.001**
No	71 (19.83)	50 (27.93)	21 (11.73)		
Yes	287 (80.17)	129 (72.07)	158 (88.27)		
BMI, kg/m^2	23.56 ± 3.64	23.20 ± 3.74	23.91 ± 3.51	−1.841	0.066
HbA1c, %	6.96 ± 1.88	5.89 ± 0.68	8.03 ± 2.08	−13.014	**<0.001**
FPG, mmol/L	7.05 ± 2.91	5.17 ± 0.80	8.93 ± 3.03	−16.050	**<0.001**

Note: Categorical data are expressed as number and proportion (n, %), and p values were derived by Chi-square test. Continuous variables are expressed as mean ± SD and p values were derived by *t*-test.

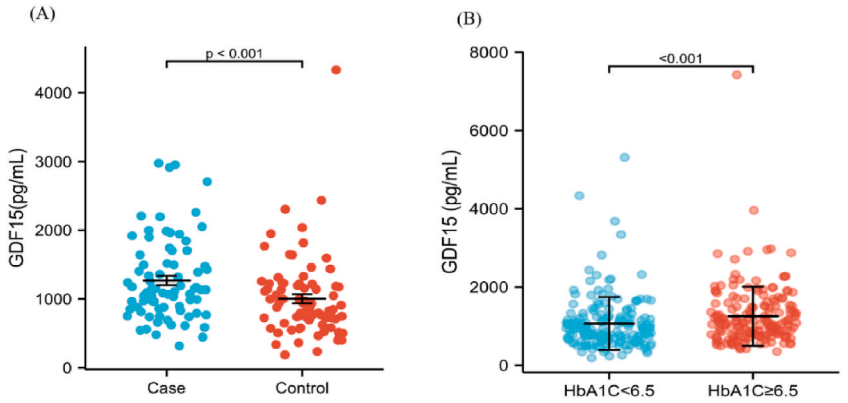

Fig. 1. (A) Differences in serum GDF-15 levels between T2DM patients and controls (B) Correlation of serum GDF-15 levels with glycated hemoglobin.

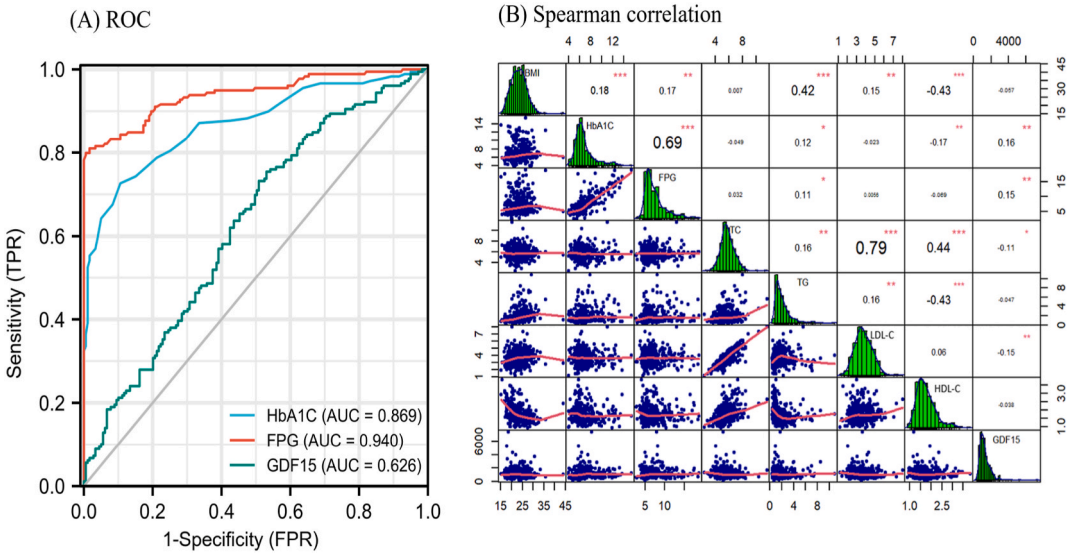

Fig. 2. (A) Receiver operating characteristic curve (ROC) to evaluate the potential of serum GDF-15 as a T2DM marker. (B) Correlation analysis of serum GDF-15 and clinical indicators. The distribution of each variable is shown on the diagonal. The bottom of the diagonal shows a binary scatter plot with fitted lines, and the top of the diagonal is the correlation value plus significance level (indicated by asterisks). Each significance level is associated with a sign: p-value (0.001, 0.01, 0.05) assigns as ("***", "**", "*").

Table 2
Correlation between serum GDF-15 levels and T2DM risk.

Serum GDF-15	Model 1		Model 2	
	OR (95%*CI*)	*p*	*AOR* (95%*CI*)	*p*
Q1	Ref.		Ref.	
Q2	2.478 (1.346–4.561)	**0.004**	3.585 (1.820–7.063)	**<0.001**
Q3	2.768 (1.504–5.094)	**0.001**	4.343 (2.162–8.727)	**<0.001**
Q4	3.416 (1.844–6.328)	**<0.001**	6.526 (3.112–13.687)	**<0.001**
P for trend		**<0.001**		**<0.001**

Note:The data were presented as odds ratio (OR) and 95 % confidence interval (CI) using logistic regression analysis. Model 1 unadjusted covariates. Model 2 adjusted for age, gender, smoking, drinking, BMI and hypertension. AOR, adjusted odd ratio.

test.

We employed logistic regression modeling to evaluate the association between specific GDF-15-related SNPs (rs1059519, rs1059369, rs1804826, and rs1054564) and the risk of T2DM under several genetic models (dominant, recessive, and co-dominant),

while adjusting for age, sex, smoking, drinking, BMI, and hypertension. The outcomes revealed that individuals with GDF-15 rs1054564 GC + CC genotype demonstrate a significantly increased risk of T2DM compared to those with GG genotype (OR = 1.724, 95 % CI: 1.046–2.841, $p = 0.033$), suggesting that carrying the C allele at rs1054564 may increase the risk of T2DM. The remaining SNP genotypes demonstrated no significant association with the risk of T2DM ($p > 0.05$), as shown in Table 3.

3.4. Association between GDF-15-related SNPs with sGDF-15, FPG and HbA1c

The recessive genetic model revealed that rs1059519 C allele was negatively associated with FPG (β recessive = −0.607, $p = 0.047$) and HbA1c (β recessive = −0.456, $p = 0.020$). According to the association analysis of the additive model, more rs1804826 T alleles are found to be correlated with a higher serum level of GDF-15 (β additive = 113.318, $p = 0.026$). We also found a positive correlation between rs1054564 C alleles and sGDF-15 levels (β additive = 247.282, $p = 0.001$, β dominant = 286.109, $p = 0.001$), as shown in Table 4.

3.5. Sensitivity analysis

To further verify that the association of GDF-15-related SNPs with FPG and HbA1c is not affected by age, we excluded individuals aged <50 years (n = 46) and performed sensitivity analyses. The results demonstrated a negative association between the rs1059519 polymorphism and FPG (β recessive = −0.6927, $p = 0.010$) and HbA1c (β recessive = −0.563, $p = 0.014$) in recessive genetic model, which is consistent with the findings observed in the total population (Table S2).

4. Discussion

The aims of this study was to evaluate serum levels of GDF-15 in T2DM patients and investigate the association between GDF-15 gene polymorphisms and the risk of T2DM in a Chinese Yao population. A case-control study with 179 T2DM patients and 179 healthy controls was conducted, along with sex- and age-matching. We found that compared to control participants, T2DM patients had much higher serum levels of GDF-15. And GDF-15 gene polymorphisms were associated with T2DM risk and also with sGDF-15, FPG, and HbA1c.

Table 3
Logistic analysis of GDF-15 SNP genotype and T2DM risk under various genetic models.

SNP	Polymorphism	Controls	T2DM	*AOR* (95%*CI*)	*p*
rs1059519 G/C					
Co-dominant model	GG	21 (11.86)	25 (14.12)	Ref.	
	CG	74 (41.81)	82 (46.33)	0.924 (0.477–1.791)	0.815
	CC	82 (46.33)	70 (39.55)	0.711 (0.366–1.382)	0.315
Dominant model	GG	21 (11.86)	25 (14.12)	Ref.	
	CG + CC	156 (88.14)	152 (85.88)	0.812 (0.435–1.514)	0.513
Recessive model	GG + CG	95 (53.67)	107 (60.45)	Ref.	
	CC	82 (46.33)	70 (39.55)	0.756 (0.495–1.156)	0.197
rs1059369 T/A					
Co-dominant model	TT	67 (38.06)	65 (36.72)	Ref.	
	TA	85 (48.30)	80 (45.20)	0.976 (0.617–1.544)	0.917
	AA	24 (13.64)	32 (18.08)	1.349 (0.717–2.537)	0.353
Dominant model	TT	67 (38.07)	65 (36.72)	Ref.	
	TA + AA	109 (61.93)	112 (63.28)	1.059 (0.687–1.631)	0.796
Recessive model	TT + TA	152 (86.36)	145 (81.92)	Ref.	
	AA	24 (13.64)	32 (18.08)	1.367 (0.767–2.439)	0.289
rs1804826 G/T					
Co-dominant model	GG	67 (38.73)	61 (34.66)	Ref.	
	GT	82 (47.40)	83 (47.16)	1.125 (0.708–1.788)	0.619
	TT	24 (13.87)	32 (18.18)	1.443 (0.765–2.723)	0.257
Dominant model	GG	67 (38.73)	61 (34.66)	Ref.	
	GT + TT	106 (61.27)	115 (65.34)	1.198 (0.774–1.854)	0.418
Recessive model	GG + GT	149 (86.13)	144 (81.82)	Ref.	
	TT	24 (13.87)	32 (18.18)	1.351 (0.757–2.412)	0.308
rs1054564 G/C					
Co-dominant model	GG	139 (78.54)	124 (70.06)	Ref.	
	GC	35 (19.77)	47 (26.55)	1.557 (0.940–2.578)	0.085
	CC	3 (1.69)	6 (3.39)	2.213 (0.540–9.075)	0.27
Dominant model	GG	139 (78.53)	124 (70.06)	Ref.	
	GC + CC	38 (21.47)	53 (29.94)	**1.724(1.046–2.841)**	**0.033**
Recessive model	GG + GC	174 (98.31)	171 (96.61)	Ref.	
	CC	3 (1.69)	6 (3.39)	2.000 (0.491–8.158)	0.334

Note: The data were presented as odds ratio (OR) and 95 % confidence interval (CI) using logistic regression analysis. T2DM, Type 2 diabetes. All data adjusted for age, gender, smoking, drinking, BMI and hypertension.

Table 4
Association between GDF 15 SNP genotypes and sGDF-15, FPG, and HbA1c.

SNP/Genetic model	sGDF-15		FPG		HbA1c	
	β	*p*	*β*	*p*	*β*	*p*
rs1059519 G/C						
Additive model	−74.892	0.157	−0.431	0.051	−0.259	0.071
Dominant model	−157.15	0.145	−0.476	0.291	−0.071	0.810
Recessive model	−71.045	0.332	−0.607	**0.047**	−0.456	**0.020**
rs1059369 T/A						
Additive model	87.522	0.093	0.07	0.749	−0.036	0.800
Dominant model	93.598	0.213	0.008	0.98	0.006	0.978
Recessive model	154.663	0.120	0.241	0.563	−0.139	0.604
rs1804826 G/T						
Additive model	113.318	**0.026**	0.084	0.702	−0.027	0.849
Dominant model	141.535	0.055	0.032	0.920	0.038	0.853
Recessive model	163.68	0.091	0.248	0.553	−0.161	0.548
rs1054564 G/C						
Additive model	247.282	**0.001**	0.434	0.150	0.147	0.448
Dominant model	286.109	**0.001**	0.48	0.167	0.222	0.321
Recessive model	325.027	0.158	0.743	0.441	−0.201	0.745

Note: Linear regression analysis was conducted and adjusted for age, gender, smoking, drinking, BMI and hypertension. sGDF-15, serum levels of growth differentiation factor-15.

In this study, sGDF-15 levels were greater in T2DM patients compared with controls, also greater in those with HbA1c $\geq$ 6.5 % compared to those with HbA1c $<$ 6.5 %. GDF-15 tends to be compensatory in inflammatory response and may have a protective effect [14], and may be affected by FPG levels. Previous studies have found that GDF-15 levels increased after glucose tolerance tests, suggesting that high glucose load or changes in insulin levels can stimulate GDF-15 secretion [15]. Interestingly, our results showed that the sGDF-15 levels were significantly positively correlated with both FPG and HbA1c, and the AUC value was 0.626. This study is similar to several studies about sGDF-15 in patients with diabetes [16,17]. It was found that sGDF-15 levels were previously reported to be positively correlated with HbA1c and FPG [18]. Elevated sGDF-15 levels are associated with an increased risk of diabetes, and GDF-15 may serve as a novel biomarker to partially replace oral glucose tolerance tests [16]. An Indian study found that sGDF-15 levels were significantly associated with HbA1c, fasting glucose, and IR status, indicating that the sGDF-15 is a novel biomarker for predicting diabetes [17]. Moreover, a case-control study in non-obese individuals found that non-obese subjects with impaired fasting glucose and newly diagnosed diabetes had significantly higher GDF-15 levels than subjects with normal glucose tolerance, and that HbA1c was independently associated with GDF-15 levels [19]. GDF-15 is required for Th2 cytokine (IL-4, IL-13) -induced glucose intolerance in mice [20], thus, may regulate Th2 cells and then influence diabetes risk. Endoplasmic reticulum (ER) stress contributes to pancreatic β cell apoptosis in diabetic patients. Xu et al. [21] found that in INS-1 cells knocked out by GDF-15 and isolated islets of GDF-15 knocked out mice, ER stress-induced apoptosis was significantly reduced, and the loss of GDF-15 significantly delayed the development of diabetes in mice. Additionally, Lee et al. [20] used RNA seq analysis to screen induction factors in adipocyte culture through recombinant IL-13, and found that GDF-15 is the key underlying factor of IL-13-induced glucose intolerance, and IL-13 will activate the STAT6 pathway activated by Janus kinase, increasing GDF-15 secretion. The relationship between GDF-15 and glucose metabolism remains controversial and needs to be further investigated in future functional studies; for example, researchers could use a mouse model of diabetes to discuss the mechanism of GDF-15 in disease occurrence or progression.

Several studies have evaluated the relationship between GDF-15 gene polymorphism and human diseases [22,23], including gene polymorphism and the risk of DM [24]. The SNP analysis in this study showed that the risk of T2DM of rs1054564 GC and CC genotypes was higher than that of GG genotypes, which was consistent with the results of previous studies. Teng MS et al. [25] found that the rs1054564-C allele may significantly alter the binding affinity of HA-Mir-1233-3p, resulting in loss of inhibition, while evidence suggests that GDF-15 is a direct target of Mir-1233-3p, and miR-1233 plays a role in multiple diseases, including diabetes [26]. For example, it is a potential biomarker for cancer and cardiovascular disease [27,28], and its overexpression in the placenta significantly reduces the proliferation and invasion capacity of trophoblast cells in hypertensive diseases of pregnancy [29]. These results therefore imply the existence of a feedback mechanism in which miR-1233 transcription is increased to compensate for elevated GDF-15 levels under diabetic conditions. There are few studies on GDF-15 gene polymorphism and T2DM, and gene-gene and gene-environment interaction analysis are needed to reveal the role of GDF-15 gene polymorphism in the etiology of T2DM.

In this study, we also found that in the dominant model, people carrying rs1059519 C allele had lower FPG levels, indicating that people carrying G allele were more likely to have elevated FPG and HbA1c levels. Previous study has shown that the polymorphism of rs1059519 was correlated with the level of plasma MIC-1 (GDF-15), and the level of MIC-1 in GG genotype was significantly higher than that in CC genotype [30]. A study of hypertensive patients in China found that rs1059519 G allele have significantly increased plasma levels of GDF-15 [31]. No correlation was found between rs1059519 polymorphism and sGDF-15 level in this study, which possibly due to the SNP sample size. Additionally, we found that the rs1804826 T allele and rs1054564 C allele were positively correlated with sGDF-15 levels, which was consistent with the results of several studies [32,33]. Patients with the rs1804826 GT/TT genotype were shown to have higher serum GDF-15 levels compared with patients with the GG genotype [34], researchers speculated that rs1804826 G/T polymorphism (located in exon 2 and leading to synonymous variant molecular results) may have a direct effect

on mRNA cleavage and thus affect the production of GDF-15. Another possible explanation is that the expression of serum GDF-15 is inducible and its expression increases after stimulation. Furthermore, among the SNPs near the 3′UTR of the GDF-15 gene, rs1054564 showed the most significant association with circulating GDF-15 levels [33]. Missense variants of rs1054564 in promoter regions in pin-linked disequilibrium have previously been associated with increased transcriptional activity and elevated levels of circulating GDF-15 [35], and the rs1054564 polymorphism was associated with circulating GDF-15 levels in a cohort of 1442 prostate cancer patients [32]. In addition, variants of SNP rs1054564 differentially modulated hsa-miR-1233-3p mediated translation inhibition, increased luciferase expression and decreased binding to hsa-miR-1233-3p suggest that individuals carrying the secondary rs1054564-C allele may exhibit elevated GDF-15 protein expression [25]. In pathological conditions where GDF-15 levels are already high, such as chronic systemic inflammation, the presence of the rs1054564 C allele may make carriers more susceptible to adverse disease outcomes and poor prognosis [36–38]. Although the directionality of the association between SNP genotypes and GDF-15 concentrations was consistent across studies, there was allelic effect heterogeneity. Serum GDF-15 levels may be determined by genetic and inducible factors.

Compellingly, recent work in rodents demonstrated that GDF-15 level is positively correlated with FPG and IR index [39,40]. A meta-analysis showed that variants of rs1054564 were associated with MIC-1/GDF-15 blood concentrations [41]. Both the Whitehall study [42]and XENDOS test [43] revealed that GDF-15 circulating levels were associated with a higher risk of T2DM, and higher serum GDF-15 levels tended to increase the risk of T2DM. These studies suggest that GDF-15 may also be part of a compensatory anti-inflammatory response in the development of T2DM. Based on the above findings, it can be inferred that SNP mutations can lead to increased inflammation in the body, and also affect the expression of serum GDF-15, and lead to the development of T2DM through inflammatory response. The current understanding of anti-inflammatory proteins and their genetic polymorphisms for the development of IR, beta cell dysfunction, and T2DM is still quite limited. The potential mechanisms by which these inflammatory factors regulate immune processes to improve metabolic control need to be confirmed by further prospective and mechanistic studies.

Interestingly, we found that T2DM group had higher prevalence of hypertension than that in controls. T2DM is frequently accompanied by obesity, which is also a risk factor for hypertension [44], approximately two-thirds of T2DM patients have hypertension [45,46]. The sequential inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) and IR are considered major factors in the coexistence of hypertension and T2DM [47]. IR is associated with increased expression of vascular adhesion molecules, oxidative stress, inflammation, which in turn leads to sustained hypertension [48]. This could explain why our case group presented a high prevalence of hypertension. It has been demonstrated that serum GDF-15 levels are elevated in patients with hypertension, and that GDF-15 levels are positively correlated with nocturnal diastolic blood pressure [49]. Several studies supported a positive correlation between GDF-15 levels and pulmonary artery pressure, which can be employed to predict pulmonary hypertension [50–52]. Elevated serum GDF-15 have also been observed in obese women with gestational hypertension [53]. GDF-15 is a well-recognized inflammatory and stress factor whose expression is increased by pressure overload and sympathetic nervous system activation [54]. Recent studies have indicated a positive correlation between GDF-15 levels and age [55]. Furthermore, circulating GDF-15 levels have been proposed to correlate with inflammation in heart failure patients[56] [57], and cognitive function in the elderly [58]. Currently, there are few studies evaluating the relationship between sGDF-15 levels, GDF-15-related SNPs and hypertension status, which requires further research.

Our study has several strengths. First, based on the description and analysis of the association between serum GDF-15 levels with the risk of T2DM and blood glucose metabolic indexes, we further explored the association of GDF-15 SNPs (rs1059519, rs1059369, rs1804826, rs1054564) with the risk of T2DM and carbohydrate metabolic indexes. This study provides a new perspective for the study on the association between GDF-15 and the risk of T2DM. Moreover, our study found that serum GDF-15 levels were positively correlated with FPG and HbA1c, and also indicated that the polymorphisms of rs1059519 and rs1054564 genes had an impact on the risk of T2DM. These findings provide insight for in-depth research and ideas for the prevention and treatment of diabetes in individuals carrying high-risk alleles or genotypes.

There are still some shortcomings in this study. First, there are many protective and risk factors for diabetes and the mechanism is complex. Although the results of this study are similar to those of previous studies, and a model of the interaction effect of gene-environment and behavior on diabetes has been established, there are certain limitations in the presentation of results due to the limited variables included in the study. Secondly, this was a case-control study based on a retrospective cross-sectional study, which may require a larger sample size for subsequent verification.

5. Conclusion

The serum GDF-15 levels were higher in T2DM patients than that in healthy controls, and positively correlated with FPG and HbA1c. The GDF-15 rs1054564 GC + CC genotype demonstrate significantly higher T2DM risk. The rs1059519 C allele was negatively correlated with FPG and HbA1c.

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Declarations

The authors declare no competing interests.

Ethical approval

This study was approved by the Ethics Committee of Guilin Medical University (No: 20180702-3).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

CRediT authorship contribution statement

Qiumei Liu: Writing – original draft, Methodology, Investigation, Formal analysis. **Lidong Qin:** Writing – original draft. **Yujian Liang:** Formal analysis. **Min Xu:** Data curation. **Junling Zhang:** Investigation, Data curation. **Xiaoting Mo:** Investigation, Data curation. **Xu Tang:** Investigation. **Yufu Lu:** Investigation. **Xuexiu Wang:** Investigation. **Jiejing Cao:** Investigation. **Chuwu Huang:** Investigation. **Jiahui Rong:** Investigation. **Kaisheng Teng:** Investigation. **Linhai Zhao:** Investigation. **Songju Wu:** Investigation. **Lei Luo:** Investigation. **Qinyi Guan:** Investigation. **TianTian Zhang:** Investigation. **Wenjia Jin:** Investigation. **Jian Qin:** Conceptualization. **Jiansheng Cai:** Writing – review & editing. **Zhiyong Zhang:** Writing – review & editing, Supervision.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, nor do we have any professional interest or other personal nature or kind in any service that could as influencing the manuscript entitled “Correlations between growth differentiation factor 15 (GDF-15) serum levels and gene polymorphism with type 2 diabetes mellitus”. The authors also declare no competing interests.

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Appendix A. Supplementary data

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